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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/596,774	06/19/2000	Bernd Groner	4-19924C/C1C1	4601

7590 12/05/2001

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EXAMINER	
CANELLA, KAREN A	
ART UNIT	PAPER NUMBER
1642	10

DATE MAILED: 12/05/2001

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/596,774	Groner et al
Examiner	**Art Unit**
Karen Canella	1642

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3 months* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☐ Responsive to communication(s) filed on _____ .

2a) ☐ This action is FINAL. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-15* is/are pending in the application.

4a) Of the above, claim(s) *1, 8, 12, and 14* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *2-7, 9-11, 13, and 15* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). *5*
18) ☐ Interview Summary (PTO-413) Paper No(s). _____
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other:

DETAILED ACTION

1. Please note that the examiner assigned to your application has changed.

2. Acknowledgment is made of applicants election without traverse of Group II, drawn to DNA, expression of recombinant protein, vectors and host cells thereof.

3. Claims 1-15 are pending. Claims 4-6, 9-11 and 15 have been amended. Claims 1, 8, 12 and 14, drawn to non-elected inventions, are withdrawn from consideration. Claims 2-7, 9-11, 13 and 15 are examined on the merits.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 1, 3 and 4 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

(A)Claim 1 is dependent on a non-elected claim.

(B)Claim 3 specifies "wherein the antigen binding domain is a single chain antibody, particularly, the single chain antibody designated FRP5. It is not clear whether the claim is limited to only FRP5 or encompasses all single chained antibodies. For purpose of examination, the claim will be limited to FRP5. Further, it is not clear if the FRP5 antibody refers to a bifunctional antibody of claim 2, or the antigen binding domain of part 1 of claim 2.

(C)Claim 4 specifies: "an immunoglobulin-like hinge region" and it is not clear how an "immunoglobulin-like" hinge region differs from an immunoglobulin hinge region. As the specification teaches that the hinge region is necessary to separate the antigen binding portion of the chimeric protein from the receptor part in order to impart greater flexibility to the antigen binding portion, and protein spacer will be considered as immunoglobulin-like.

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claim 3 is rejected under 35 U.S.C. § 112, first paragraph, as failing to provide an adequate written description of the invention and failing to provide an enabling disclosure without complete evidence either that the claimed biological materials are known and readily available to the public or complete evidence of the deposit of the biological materials.

The specification lacks complete deposit information for the deposit of a cell line producing the antibody FRP5. It is not clear that a cell line possessing the identical properties of FRP5 is known and publicly available or can be reproducibly isolated from nature without undue experimentation.

Exact replication of a cell line is an unpredictable event and it is unclear that one of skill in the art could derive recombinant cell lines secreting single chained antibodies identical to those claimed. Undue experimentation would be required to screen all of the possible antibody species to obtain the claimed single chained antibody..

Because one of ordinary skill in the art could not be assured of the ability to practice the invention as claimed in the absence of the availability of the claimed antibody, a suitable deposit of a cell line producing FRP5 for patent purposes, evidence of public availability of the claimed FRP5 or amendment of the claim to incorporate a SEQ ID NO is required.

If the deposits is made under the provisions of the Budapest Treaty, filing of an affidavit or declaration by applicant or assignees or a statement by an attorney of record who has authority and control over the conditions of deposit over his or her signature and registration number stating that the deposit has been accepted by an International Depository Authority under the provisions of the Budapest Treaty, that all restrictions upon public access to the deposits will be irrevocably removed upon the grant of a patent on this application and that the deposit will be replaced if viable samples cannot be dispensed by the depository is required. This requirement is

necessary when deposits are made under the provisions of the Budapest Treaty as the Treaty leaves this specific matter to the discretion of each State.

If the deposit is not made under the provisions of the Budapest Treaty, then in order to certify that the deposits comply with the criteria set forth in 37 CFR 1.801-1.809 regarding availability and permanency of deposits, assurance of compliance is required. Such assurance may be in the form of an affidavit or declaration by applicants or assignees or in the form of a statement by an attorney of record who has the authority and control over the conditions of deposit over his or her signature and registration number averring:

(a) during the pendency of this application, access to the deposits will be afforded to the Commissioner upon request:

(b) all restrictions upon the availability to the public of the deposited biological material will be irrevocably removed upon the granting of a patent on this application:

© the deposits will be maintained in a public depository for a period of at least thirty years from the date of deposit or for the enforceable life of the patent of or for a period of five years after the date of the most recent request for the furnishing of a sample of the deposited biological material, whichever is longest; and

(d) the deposits will be replaced if they should become nonviable or non-replicable.

Amendment of the specification to recite the date of deposit and the complete name and address of the depository is required. As an additional means for completing the record, applicant may submit a copy of the contract with the depository for deposit and maintenance of each deposit.

If deposits are made after the effective filing date of the application for patent in the United States, a verified statement is required from a person in a position to corroborate that the antibody described in the specification as filed is the same as that produced by the cell line deposited in the depository, stating that the deposited material secretes an antibody that is identical to the biological material described in the specification and was in the applicant's possession at the time the application was filed.

Applicant's attention is directed to In re Lundak, 773 F.2d. 1216, 227 USPQ 90 (CAFC 1985) and 37 CFR 1.801-1.809 for further information concerning deposit practice.

8. Claims 2, 4-7, 9-11, 13 and 15 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Claim 2 is broadly drawn to a DNA encoding a bifunctional protein comprising an antigen binding domain derivable from a monoclonal antibody directed against a suitable antigen on a tumor cell. However, the written description in this case only sets forth SEQ ID NO:5, which comprises only the antigen binding domain from an anti-Erb-B2 antibody, and therefore the written description is not commensurate in scope with the claims drawn to all possible antigen binding regions derived from monoclonal antibodies which bind to tumor antigens.

Vas-Cath Inc. V. Mahurkar, 19 USPQ2d 1111, clearly states that applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the written description inquiry, whatever is now claimed. (See page 1117). The specification does not clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed. (See Vas-Cath at page 1116).

Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 USC 112 is severable from its enablement provision (see page 115).

In The Regents of the University of California v. Eli Lilly (43 USPQ2d 1398-1412), the court held that a generic statement which defines a genus of nucleic acids by only their functional activity does not provide an adequate written description of the genus. The court indicated that while Applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a representative number of DNA molecules, usually defined by a nucleotide sequence, falling within the scope of the claimed genus. At section B(1), the court states that an adequate written description of a DNA requires a precise definition, such as by structure, formula, chemical name, or physical properties, not a

mere wish or plan for obtaining the claimed chemical invention. Thus as the broad genus of antigen binding domains derivable from a monoclonal antibodies directed against suitable target antigens on tumor cells is supported by only one example in which an antigen binding domain has been derived from an antibody directed against the erbB-2 antigen, this does not constitute an adequate description of a genus of DNA encoding a bifunctional molecule comprising a multitude of antigen binding domains derivable from monoclonal antibodies directed against tumor antigens.

Adequate written description requires more than a mere statement that it is part of the invention The nucleic acid itself is required. See Fiers v. Revel, 25 USPQ 2d 1601 at 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Lts., 18 USPQ2d 1016.

Therefore, only the DNA comprising SEQ ID NO:5, but not the full breadth of the claims meets the written description provision of 35 USC 112, first paragraph.

Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

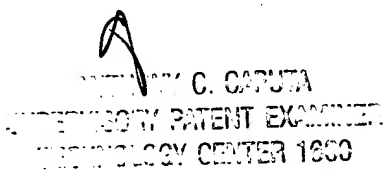
This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103© and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

10. Claims 2-7, 9-11, 13 and 15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Stancovski et al, (Journal of Immunology, 1993, Vol. 11, pp. 6577-6582) in view of Brocker et al (Eur. J. Immunology, 1993, Vol. 23, pp. 1435-1439, reference AA of the IDS filed 9/22/00) and Horgan et al (Journal of Immunology, 1993, Vol. 150, pp. 5400-5407). Claim 2 is drawn to a DNA encoding a bifunctional protein comprising an antigen binding domain derived from a monoclonal antibody directed against a tumor cell antigen, a hinge region, and a zeta chain of the TCR. Claim 15 is drawn to a vector comprising said DNA. Claim 3 specifies that the antigen binding domain is derived from FRP5. Claim 4 specifies that the hinge region is an immunoglobulin-like hinge region, which is being interpreted as a protein spacer region for the reasons stated in paragraph 5(B) above. Claims 5 specifies that the zeta chain comprises a transmembrane and cytoplasmic domain. Claims 6, 11, 7 and 13 embody the host cell, compositions of matter comprising the host cell, the host cell as a cytotoxic lymphocyte, and a CTL for use in a method of treating cancer, respectively. Please note that the CTL of claim 13 is identical in scope to the host cell of claim 7, as intended use does not constitute a patentable difference in product claims. Claim 9 is drawn to a process of producing a CTL having MHC-tumor cell specificity. Claim 10 is drawn to a method of producing the chimeric protein comprising recombinant expression in a host cell. Stancovski et al teach a host cells comprising a vector encoding a chimeric protein comprising the antigen binding domain of anti-Her2 antibodies and the zeta chain of the TCR complex. Stancovski et al teach that T cells transfected with the DNA encoding the chimeric protein were able to lyse Her2 target cells. Stancovski et al do not teach that a hinge region or spacer peptide is necessary for activity of the chimeric protein. Brocker et al teach host cells comprising a vector encoding a chimeric protein comprising antigen binding regions derived from a monoclonal antibody, a hinge region and the transmembrane and cytoplasmic regions of the TCR zeta chain. Brocker et al teach that binding to the target antigen was successful in activating T cells transfected with said vector and that antigen was recognized in a non-MHC restricted context (page 1438, second column, line 4-8) Brocker et al do not teach an antigen binding region derivable from a monoclonal antibody directed against a tumor antigen. Horgan et al teach that chimeric antibodies comprising the hinge region of IgG1 bound

target antigen better than chimeric antibodies which had deleted hinge regions. It would have been *prima facia* obvious to one of ordinary skill in the art at the time the claimed invention was made to incorporate the DNA encoding the hinge region of Brocker et al into the vector of Stancovski et al. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the teachings of Horgan et al on the enhanced affinity of chimeric antibodies containing IgG1 hinge region, vs chimeric antibodies having said hinge region deleted, and the teachings of Brocker et al on the effective activation of T cells recombinantly expressing a vector comprising an antibody binding region, a hinge region and a zeta chain.

Conclusion

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen Canella whose telephone number is (703) 308-8362. The examiner can normally be reached on Monday through Friday from 8:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached on (703) 308-3995. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.



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Patent Examiner, Group 1642
November 29, 2001